## Phylogeny

• Kinase classification: Ca²⁺/calmodulin-regulated protein kinase (CaMK) group, myosin light-chain kinase (MLCK) family, Unc-89/obscurin-related dual-kinase subfamily (fleming2021exploringobscurinand pages 1-2, luo2021striatedpreferentiallyexpressed pages 1-2).  
• Evolutionary origin: vertebrate duplication of OBSCN generated SPEG; the second kinase domain (SK2) shows marked divergence in the ATP-binding region (grogan2020doublethetrouble pages 6-8).  
• Ortholog distribution: Homo sapiens SPEG, Mus musculus Speg, Rattus norvegicus Speg, Gallus gallus Speg, Xenopus laevis Speg; Danio rerio paralogues spega and spegb (unknownauthors2020elucidatingtherole pages 12-16).  
• Invertebrate context: no direct orthologue; analogous architecture provided by Caenorhabditis elegans UNC-89/twitchin (luo2021striatedpreferentiallyexpressed pages 2-4).

## Reaction Catalyzed

Protein-L-Ser/Thr + ATP ⇌ Protein-L-Ser/Thr-phosphate + ADP (fleming2021exploringobscurinand pages 1-2).

## Cofactor Requirements

Not experimentally confirmed; Mg²⁺ presumed as for other MLCK-family enzymes (li2023integratedmultiomicsapproach pages 25-29).

## Substrate Specificity

• Consensus phosphorylation motif: not determined; SPEG absent from the Johnson 2023 serine/threonine kinase atlas (fleming2021exploringobscurinand pages 11-12).  
• Experimentally validated targets and sites  
– Junctophilin-2, sites not mapped (grogan2020doublethetrouble pages 6-8).  
– SERCA2a Thr484 (luo2021striatedpreferentiallyexpressed pages 4-5).  
– RyR2 Ser2367 (lee2023speginteractionsthat pages 1-2).  
– RyR1 Ser2902 (li2023integratedmultiomicsapproach pages 1-5).  
– SPEG autophosphorylation within kinase-1 (grogan2020doublethetrouble pages 6-8).

## Structure

• Domain organisation (N→C): truncated Ig-like array → multiple fibronectin type-III domains → kinase-1 (SK1) → low-complexity inter-kinase linker → kinase-2 (SK2) → short C-terminal tail (grogan2020doublethetrouble pages 6-8, lee2023speginteractionsthat pages 1-2).  
• Catalytic motifs: SK1 and SK2 each retain VAIK, HRD and DFG triads consistent with catalytic competence (fleming2021exploringobscurinand pages 11-12).  
• 3D data: no PDB structures; homology models and AlphaFold prediction show canonical bilobed kinase folds with intact catalytic and regulatory spines (fleming2021exploringobscurinand pages 1-2).  
• Unique element: inter-kinase linker lacks the autophosphorylation observed in obscurin, indicating divergent regulation (fleming2021exploringobscurinand pages 1-2).

## Regulation

• Autophosphorylation: kinase-1 undergoes cis autophosphorylation; kinase-2 minimal (grogan2020doublethetrouble pages 6-8).  
• Upstream phosphorylation  
– Akt/PKB: Ser2461, Ser2462, Thr2463; enhances catalytic activity (fleming2021exploringobscurinand pages 11-12).  
– CaMKII: Ser2130 (human numbering); modulates cardiac function (fleming2021exploringobscurinand pages 11-12).  
• Calmodulin interaction: C-terminal CaM-binding segment present; kinase-1 activity partly CaM-independent (grogan2020doublethetrouble pages 6-8).  
• No reported ubiquitination, sumoylation or acetylation (fleming2021exploringobscurinand pages 11-12).

## Function

• Isoform expression: SPEGβ (~355 kDa) and SPEGα (~250 kDa) dominant in cardiac and skeletal muscle; APEG-1 in arterial smooth muscle; BPEG in brain (luo2021striatedpreferentiallyexpressed pages 1-2).  
• Subcellular localisation: Z-disk and triad/dyad regions of the sarcoplasmic reticulum (grogan2020doublethetrouble pages 6-8, lee2023speginteractionsthat pages 1-2).  
• Interacting partners  
– RyR2 and RyR1 (grogan2020doublethetrouble pages 6-8, li2023integratedmultiomicsapproach pages 25-29).  
– Junctophilin-2 (quick2017speg(striatedmuscle pages 1-3).  
– SERCA2a (luo2021striatedpreferentiallyexpressed pages 4-5).  
– MTM1 (li2023integratedmultiomicsapproach pages 36-42).  
– Desmin (luo2020spegbindswith pages 1-1).  
– CMYA5, FSD2, Esterase-D (lee2023speginteractionsthat pages 1-2).  
– Dynamin-2 (luo2021striatedpreferentiallyexpressed pages 5-7).  
• Biological roles  
– Maintenance of triad and T-tubule architecture via Junctophilin-2 phosphorylation and desmin interaction (quick2017speg(striatedmuscle pages 1-3, luo2020spegbindswith pages 1-1).  
– Regulation of excitation–contraction coupling: inhibitory RyR2 Ser2367 phosphorylation and stimulatory SERCA2a Thr484 phosphorylation (lee2023speginteractionsthat pages 1-2, luo2021striatedpreferentiallyexpressed pages 4-5).  
– Modulation of skeletal muscle RyR1 via Ser2902 phosphorylation (li2023integratedmultiomicsapproach pages 1-5).  
– APEG-1 supports arterial smooth-muscle cell growth and differentiation (luo2021striatedpreferentiallyexpressed pages 1-2).

## Inhibitors

No specific inhibitors reported (fleming2021exploringobscurinand pages 1-2, grogan2020doublethetrouble pages 6-8).

## Other Comments

• Disease associations: autosomal-recessive loss-of-function variants cause centronuclear myopathy with or without dilated or left-ventricular non-compaction cardiomyopathy (luo2021striatedpreferentiallyexpressed pages 4-5, wang2017insightsfromgenotype–phenotype pages 10-14).  
• Pathogenic variants: nonsense, frameshift and in-frame deletions; truncations disrupting the MTM1-interaction region correlate with severe cardiac phenotypes (wang2017insightsfromgenotype–phenotype pages 10-14).  
• Expression in disease: SPEG mRNA reduced by ~83 % in failing human hearts (quick2017speg(striatedmuscle pages 1-3).

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